Editorial
A COMET lost

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In view of the striking similarity in the mortality and morbidity benefits reported in the three major trials examining the role of beta-adrenergic blocking agents in heart failure due to systolic dysfunction (MERIT-HF[1], CIBIS-II[2] and COPERNICUS[3]), one might wonder why it is necessary to carry out a trial comparing one drug with another. All three trials ended up with an approximate 35% decrease in mortality with slightly different patient populations. And if you did wish to compare the drugs used in these trials, why would you not give the same drug formulation and the same dose of the drugs used in the large-scale trial in order to strike a comparison. This is the criticals question that arises from the COMET trial[4]. Instead, the investigators chose to compare the standard dose of carvedilol to a different drug formulation of metoprolol used in MERIT-HF and a different and lower dose of that formulation that had been used in the major studies in the past. Why the investigators made such a grievous error and used metoprolol tartrate IR at a reduced dose of 50 mg bid rather than metoprolol succinate CR at 200 mg daily which was used in MERIT-HF or even a higher dose of metoprolol IR, is not readily apparent. The investigators of COMET, rather than providing the medical world with a comparative study of the two major drugs with differing pharmacologic characteristics, have instead told us something we already knew. In order to achieve the profound mortality effects of beta-blockade reported in the three randomized trials, one must up-titrate to the maximal dose tolerated. With data published by the US Carvedilol study[5] and from CIBIS-II and I experience, it is clear that the higher the dose, the greater the effect. In addition, studies from the MERIT-HF trials clearly indicate that there is a considerable variability in individual heart failure patient's heart rate response to beta-blockade[6]. This maximal dose has a wide variation from one patient to another in heart failure, although the percent patients achieving maximal dose is similar in the three studies.

In order to justify the dose of metoprolol used in COMET the investigators have taken us on an excursion into a pharmacologic world of Alice in Wonderland in order to convince the readers that small is large. In an attempt to apply their observation on low-dose metoprolol IR to the large mortality trial of CIBIS-II and MERIT-HF, the authors of COMET attempt to convince the reader that 100 mg daily of metoprolol IR with a mean dose of 98 mg% is the same as 200 mg of metoprolol CR of 158 mg% used in MERIT-HF. Much of this argument hinges on the supposed similar heart rate achieved with the two drugs. This in spite of the fact that in COMET carvedilol had a greater decrease in both heart rate and blood pressure than that achieved with metoprolol IR. The authors also attempt to convince us that no further heart rate benefit could have been achieved with 200 mg of metoprolol CR than with 100 mg of metoprolol IR. However it is clear from studies in heart failure patients by Andersson et al.[7], that metoprolol CR 200 mg has a greater effect on heart rate and blood pressure at rest and during exercise than even observed with 150 mg daily of metoprolol IR. A number of investigators including Metra et al.[8] compared the physiologic effects of 25 to 50 mg bid of carvedilol to 50 to 100 mg bid daily of metoprolol IR with an average dose of 44 ± 17 mg/day of carvedilol and 115 ± 56 mg/day of metoprolol IR. They demonstrated that carvedilol has a greater effect

on exercise heart rate than metoprolol IR does even at this dose of metoprolol IR. The under-dosing of the metoprolol IR arm could well explain the lower mortality rate in the metoprolol IR patients in COMET when compared to MERIT-HF (10 vs 7.4%, respectively).

In addition the authors misinterpret the analysis of dose published by the MERIT-HF investigators[7]. That studies indicated that during up-titration to full tolerated dose, there was a wide variation in sensitivity of patients to metoprolol CR and presumably all other beta-blockers. Up-titration was predominately limited by slow heart rate, which averaged 67 b/min in both the high and low dose. Up-titration to a heart rate of 67 b/min was achieved in one third of the patients in MERIT-HF with less than 100 mg daily (mean dose of 76 mg). However two thirds of the patients required up-titration to 200 mg (mean dose 192 mg) in order to achieve the same heart rate. If one did not up-titrate, almost one half of the patients would have only reached a heart rate of approximately 72 b/min, far from the heart rate decrease reached in the three major trials. Regardless of the dose, the benefit was the same as long as metoprolol CR was up-titrated to the maximum effect, which occurred at an average heart rate of 67 b/min in both the high and low-dose groups. Although the patients who reached the heart rate of 67 b/min with lower doses were generally older, had lower ejection fraction and had more severe heart failure, these demographic characteristics did not provide definitively distinguishing demographic characteristics. Most physicians treating patients with heart failure have been aware of this clinical phenomenon. The particular reason for this is not certain but may be related to the relative sensitivity of beta-receptors to beta-blockade. These observations are essential to the management of patients with heart failure regardless of the drug used and is the method used in the major randomized trials to achieve their mortality and morbidity benefit. It is unfortunate that the authors did not understand this very important message in regard to beta-blocker therapy since it carries a very important message both to the patient and to the practitioner.

It is unfortunate that the COMET investigators have spent so much time and energy on this poorly designed study. What COMET has given us is a trial in which one beta-blocker, carvedilol, was given to a maximum dose and compared to a formulation of metoprolol at a low and insufficient dose. A more appropriate comparison of selective $beta_1$-blockade to non-selective beta-blockade could have been of some interest. The fact that the investigators have created a false message in regard to the need to up-titrate beta-blockers to achieve maximum clinical effect is regrettable. Nevertheless, the observation that an efficacy of beta-blocker therapy is dose-dependent is important, regardless of the agent used.

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